Critical Review Form
Therapy

Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost. 2014 Apr.

Objective: **to "test if tenecteplase increases the probability of a favorable composite patient-oriented outcome after submassive PE [pulmonary embolism]." (p. 459)**

Methods: **This multicenter, randomized, double-blinded, placebo-controlled trial was conducted at 8 US academic medical centers. Patients older than 17 years of age with PE diagnosed on CT pulmonary angiogram within 24 hours with normal systolic blood pressure (SBP) and evidence of right ventricular strain were eligible for enrollment. Right ventricular strain was defined as either hypokinesis on echocardiography, elevated troponin I or T, or elevated brain natriuretic peptide (BNP >90 pg/mL or NT proBNP > 900 pg/mL). Patients with hypotension (SBP < 90 mm Hg), an inability to walk, contraindications to thrombolysis, or end-stage conditions were excluded.**

All patients received low molecular weight heparin, either enoxaparin (1 mg/kg) or dalteparin (200 U/kg) administered subcutaneously. Patients were randomized using a predetermined blocked permuted 1:1 randomization sequence linked to a unique study ID. This was used by the research pharmacist to then prepare either placebo or tenecteplase in an opaque syringe for immediate injection.

Five-day adverse outcomes were assessed, including both PE-related outcomes (death, circulatory shock defined as hypotension requiring vasopressors, and need for intubation) and treatment-related outcomes (death from hemorrhage, intracranial or intraspinal hemorrhage, active bleeding with a > 2 g/dL drop in hemoglobin requiring transfusion, and any bleeding requiring surgery, endoscopy, or intravascular treatment). At 90 days, all survivors returned for follow-up and had a transthoracic ECHO performed and interpreted by a cardiologist blinded to treatment group and outcome. Additionally, the following outcomes were assessed:

1) Recurrence of venous thromboembolism

2) Poor functional capacity defined as 2 of the following being present: i) right ventricular (RV) hypokinesis or dilation, or RV systolic pressure > 45 mm Hg; ii) dyspnea at rest or inability to walk 330 meters in a 6-minute walk test; iii) severe dyspnea defined as New York Heart Association (NYHA) functional class 3 or 4.

3) Poor quality of life measured as a Physical Component Summary (SF-36) score below 30 or post-thrombotic syndrome as measured by a VEINES QOL survey < 40.

The primary outcome was a composite of: any serious adverse outcome within 5 days of enrollment, recurrent thromboembolism in 3 months, poor functional capacity at 3 months (as previously defined), a physical component summary score < 30 at 90 days, or a VEINES QOL score < 40 at 90 days.

Between August 2008 and October 2012, 643 patients meeting inclusion criteria were screened, of whom 87 (13.5%) were enrolled. The study was stopped early due to the relocation of the principle investigator. There were 40 patients randomized to tenecteplase and 43 randomized to placebo. Initial cardiac ECHO was obtained in 54 patients (65%), BNP in 69 (83%), and troponin in 83 (100%).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. Patients were randomized by a blocked, permuted 1:1 randomization sequence.
2.	Was randomization concealed (blinded)?	Yes. "Study group assignment occurred by a predetermined, blocked permuted 1 : 1 randomization sequence that was prepared by the study statistician and linked to a unique study ID number used by a research pharmacist to prepare placebo or tenecteplase in 0.9% saline in an opaque syringe." (p. 460)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The authors used an intention to treat analysis. The authors do not specifically mention any crossover (i.e. patients in the tenecteplase group who were not given tenecteplase, or patients in the placebo group who were later given thrombolytics).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. This was a small study, and hence none of the differences observed between the groups reached statistical significance. There was a trend towards a higher rate of prior MI (5% vs. 0%), surgery in the previous 6 weeks (9% vs. 3%), and a history of COPD (7% vs. 0%) in the placebo group. There was a trend towards a higher rate of active malignancy (23% vs. 9%) in the tenecteplase group, and a higher rate of malignancy under chemotherapy treatment that did reach statistical significance (12.5% vs. 0%, p = 0.01). Importantly, patients were similar with respect to the

		presence of right ventricular dysfunction on ECHO, troponin elevation, and BNP/NT proBNP elevation. Patients in the two groups were also similar with respect to frequency and location of deep venous thrombosis.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. Patients were blinded to group allocation by the use of opaque syringes.
2.	Were clinicians aware of group allocation?	No. Clinicians were blinded to group allocation by the use of opaque syringes.
3.	Were outcome assessors aware of group allocation?	Likely yes. The authors state: "Echocardiograms [performed at 3 month follow-up] were interpreted by a board-certified cardiologist who was blinded to treatment and outcome." (p. 461) They do not explicitly state whether 5-day outcome assessors were blinded, or whether those performing and interpreting the 6-minute walk test at 3 months were blinded.
4.	Was follow-up complete?	No. 5-day follow-up was performed in all patients enrolled. Complete 90-day follow-up data was obtained in 39 of 43 survivors (90%) from the placebo group and 37 of 39 survivors (94%) from the tenecteplase group. There is therefore a risk of attrition bias.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• During the initial 5 days, there were 3 adverse events in the placebo group (one patient died; 2 required intubation, vasopressors, and catheter thrombectomy) compared with 1 in the tenecteplase group (ICH resulting in death). • Among survivors at 90-day follow-up, 13 patients in the placebo group had an adverse event (30%, 95% CI 17 to 46%) vs. 5 in the tenecteplase group (12.5%, 95% CI 4 to 27%). • For the primary composite outcome, 16 out of 43 (37%, 95% CI 23 to 53%) subjects with complete follow-up

		data had an adverse outcome in the placebo group compared to 6 out of 40 (15%, 95% CI 6 to 30%) in the tenecteplase group, for an absolute risk reduction of 22% (95% CI 3.2 to 40%) and a NNT of 4.5 (95% CI 2.5 to 25). There were no deaths reported after the initial 5-day follow-up period. • The proportion of patients who remained in the ICU on day 2 was significantly higher with placebo compared with tenecteplase (20.5% vs. 5%, p = 0.03) • Hemoglobin values were not different on day 2: 12.7 ± 1.8 g/dL for placebo vs. 12.3 ± 1.8 g/dL for tenecteplase (p = 0.4). • During hospitalization, the total number of Good Clinical Practice-reportable adverse events that were not part of the main composite outcome was similar between groups, with 23 (53%) in the placebo group and 24 (55%) in the tenecteplase group.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. These were patients with submassive PE, defined as PE with signs of right heart strain but without hemodynamic compromise, treated in large US academic medical centers. Cardiac ECHO was not routinely obtained, which is similar to our clinical practice.
2.	Were all clinically important outcomes considered?	Yes. The authors considered not only mortality, but also additional patient-centered outcomes reflecting quality of life (using the Physical Component Summary (SF-36) score) and functional capacity (using a 6-minute walk test).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. Treatment with tenecteplase reduced both 5-day and 90-day adverse events. However, the primary outcome was a composite of a variety of patient-centered outcomes (e.g. death, quality of life) and surrogate outcomes (e.g. ECHO findings), and it is unclear from the report which outcomes drove the estimated effect size. Unfortunately, the study was stopped early for unforeseeable logistic reasons before the planned 200 subjects could be enrolled. In spite of this, statistical significance was reached for the primary

		outcome, though it remains unclear how to use this information.

Limitations:

1) **The trial was stopped early due to logistic reasons prior to enrolling the planned 200 subjects. While statistical significance was still reached for the primary outcome, this could represent an erroneous finding.**

2) **10% of the placebo group and 6% of the treatment group had no 90-day follow-up information (attrition bias).**

3) **The authors used a composite outcome consisting of both patient-centered outcomes (e.g. death, quality of life) and surrogate outcomes of unclear clinical significance (ECHO findings).**

4) **Despite finding improved quality of life measurements at 90 days, the authors note that "we found no difference in the frequency of right ventricular dilation or hypokinesis between groups." (p. 466)**

Bottom Line:

This small randomized, placebo-controlled trial of tenecteplase for the treatment of submassive PE found a significant reduction in the primary composite outcome of adverse events at 5-days and 90-days: ARR of 22% (95% CI 3.2 to 40%), NNT of 4.5 (95% CI 2.5 to 25). Issues related to the trial being stopped early and the use of an unweighted composite outcome limit our conclusions.